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Issues in clinical trial design

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Introduction

The last three years have witnessed dramatic changes in both our understanding of how the Human Immunodeficiency Virus (HIV) works, and in the range of options for treating HIV illness. For many people, replication of the virus can now be suppressed. Combination therapy using three or more antiviral drugs is effective in many cases in suppressing viral replication for up to two years before the emergence of resistant strains. The emergence of resistant strains signals therapeutic failure and requires a change in treatment regimen.

The changing landscape of HIV antiretroviral treatments presents important challenges to the ways in which information about HIV/AIDS drugs and their effectiveness is gathered. Combination therapy has replaced monotherapy as standard practice, and the new 'gold standard' in HIV antiretroviral therapy is undetectable viral load. At the same time, it is not known exactly which combination of drugs works best for different individuals and at different times. Many questions about the use of combination therapy remain unanswered.

There are important challenges for the future design of HIV/AIDS clinical trials. The Clinical Trials and Treatments Advisory Committee of the Australian National Council on AIDS and Related Diseases (ANCARD), is arranging a forum in conjunction with AFAO to discuss the future design of clinical trials and the future research agendas. This forum is scheduled for 3 and 4 April 1998, and this discussion paper aims to inform community debate in the lead up tothe forum.

It is not the role of AFAO to set prescriptive guidelines for the conduct of clinical trials; rather, AFAO has a responsibility to its constituents to set out concerns about the current dilemma facing research, and the sorts of questions that we would like to see answered. Establishing alternative designs for research should be a collaborative effort between the affected community and their organisations, such as AFAO and the National Association of People with HIV/AIDS (NAPWA); government (in its role as consumer protector); the medical profession (in its dual role as carer and researcher); and drug companies (in their capacity as producers of drugs).

HIV/AIDS clinical trials

Background and history

In January 1995 - almost 15 years after the first cases of HIV emerged - an important discovery was made about the virus. At the Second US National Conference on Human Retroviruses and Related Infections in Washington, DC, there was general agreement that

far from lying largely dormant during a long period of post-infection incubation, HIV is active in the host body from the time of infection. Researchers had made the discovery that each day, a person with HIV releases between 20 million and 7 billion copies of the virus into the blood. The immune system was found to be equally active in its efforts to suppress the virus, with about 2 billion CD4 cells[1] created and killed daily as a result of HIV infection. Slowly, HIV gained the upper hand, the conference was told[2] The discovery led to demands at the conference for an end to "therapeutic nihilism" and a rapid start to trials of three- and four-drug combinations.

Another promising development at that time was the development of a test to measure directly the amount of virus present in blood plasma. Viral load' tests increase the speed with which the anti-HIV effect of new drugs can be measured. Research suggests that the amount of virus in plasma is a powerful predictor of disease progression and a marker of the effects of therapy. When combined with the measurement of CD4 cell levels (to reflect the state of the immune system), the viral load test greatly aids the evaluation of new drugs.

Later, in September 1995, the results of two international drug trials were released. These were the Delta and ACTG 0175 trials and they offered the strongest evidence available at that time that combination therapy was the best way forward.[3][4] Various commentators stressed that the dramatic benefits shown in these trials would change the standard of care for PLWHA. In Australia, the National Association of People with HIV/AIDS (NAPWA) joined clinical researchers in calling for changes in the funding arrangements for antiretroviral drugs, to allow PLWHA access to a 'cocktail' of drugs. In a press release following the announcement of the trials' results , NAPWA also warned that "some clinical trials now under way in Australia and overseas which test new drugs against AZT alone should be reviewed in the light of this research. Combination therapy is the best standard of treatment and this should be reflected in the design of clinical trials."[5] In particular, this

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[1] This is a measure of immune function, and is also know as T-cell counts.

[2] Wei, X. et al (1995), 'Viral dynamics in human immunodeficiency virus type I infection', Nature, 373:117-122; Ho, D. et al (1995), 'Rapid turnover of plasma virions and CD4 lymphocytes in HIV-I infection', Nature, 373: 123-126; for reports from the Washington conference, see Hand, D. (1995), 'Second National Conference on Human Retroviruses and Related Infections: Special Conference Report', National AIDS Bulletin, 9,2: 53; Maynard, T. (1995), 'A new understanding of HIV', National AIDS Bulletin, 9,3: 10-11.

[3] The Delta trial was conducted in Australia and seven European centres. It was designed to test treatment using AZT alone with combined therapy using AZT/ddI and AZT/ddC. People who had never before taken AZT were included in one arm of the trial (Delta 1) and those who had at least three months experience of AZT were included in the second arm (Delta 2). The 3,214 participants were required to have a CD4 cell count of less than 350 to enter the trial. Delta was stopped on ethical grounds after preliminary results showed "strong evidence" that combined therapy worked better than using AZT alone in substantially improving survival times and slowing progression to AIDS. Overall, the study found, combination therapy led to a reduction in mortality of about 25 per cent. In a summary distributed to Delta investigators, the trial organisers said: "The initiation of antiretroviral chemotherapy with combinations of AZT plus ddI or ddC conferred a substantial benefit in terms of survival and progression to AIDS, compared with AZT monotherapy."

[4] The AIDS Clinical Trials Group (ACTG) is part of the American National Institute of Allergy and Infectious Diseases. ACTG 0175 compared three drugs used either in combination or alone: zidovudine (AZT), didanosine (ddI) and zalcitabine (ddC). It enrolled a total of 2,467 people, about one half of whom had never taken AZT before enrolment. Participants had an equal chance of receiving one of the following treatments: AZT alone; ddI alone; AZT and ddI; or, AZT and ddC. Overall, the trial found that combination therapy worked better than monotherapy, and that ddI worked better than AZT as a monotherapy. The US National Institutes of Health said the results "confirm the importance of careful planning in the use of antiretroviral regimens since prior antiretroviral experience may substantially influence the effectiveness of the treatment regimen."

[5] See Hand, D. (1995), 'New "gold standard" in HIV therapy boosts treatments optimism', National AIDS Bulletin 9,6: 48-49.

challenge was laid down for randomised control trials, the main research instrument used in evaluating HIV therapies.

Early in 1997, an American trial (ACTG 320) was stopped on ethical grounds after it was found that patients in the control arm of the trial, who were being treated with a combination of two drugs, were becoming sicker and dying faster than those in the second arm of the trial who were receiving a more potent triple-drug cocktail. The demise of the study is noted to have added fresh urgency to the debate over how to obtain useful results from drug tests without risking patients' lives.[6] One treatments journal reported that the decision to halt the trial marked the end of the "body count trials".[7] The trial's demise also highlights that undetectable viral load is now the new 'gold standard' for HIV treatments and clinical trials.

What are randomised control trials?

Randomised control trials (RCT) are regarded as the cornerstone of evidence-based medicine. Such trials usually involve the examination of a new medication, treatment strategy or therapeutic intervention (such as a new surgical procedure), but may also be concerned with other areas such as diet or the influence of tobacco on health.

RCTs are 'randomised' because the participants in a trial are assigned in a random fashion to the various study groups. The reasoning behind this approach is that each participant in, say, a trial of an HIV antiretroviral drug, should have an equal chance of being placed in any of the groups that make up the study as a whole. Such studies are 'controlled' in that there is usually a treatment group and a control group, where the treatment group receives a particular treatment (for example, a new type of antiretroviral drug) and the control group either receives the standard treatment or no treatment at all (placebo). At the end of the trial period, comparisons are then made between the two groups to assess the effect of a particular treatment.

RCTs are sometimes 'blind' or 'double blind'. These are techniques used to guard against possible bias on the part of the researchers or participants in assessing or reporting the effect of a treatment. Blinding is where the trial participant or the researcher is unaware of who is in the treatment group or the control group -- in other words, they are not aware of whether an individual is receiving the new treatment, or the standard treatment/placebo. Double blind is where both the participant and the researcher are unaware. An RCT which is not blinded, and where everyone knows which participants are receiving which treatments, is called an 'open label' trial. Rules for the conduct of clinical trials are based on both the need to ensure scientific validity (for example, by ensuring outcomes are not biased by other factors beyond what is being measured) and on the need for ethical conduct.

Classification of clinical trials

Clinical trials are usually classified with reference to the trials' objectives and design. On the basis of trial objectives, a classification system using phases has been developed, and is often referred to in the HIV/AIDS literature:

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[6] Cohn, J. !997) 'AIDS trials ethics questioned', *Science*, 276: 520-3 (25 April).

[7] 'ACTG 320: Last of the Body Count Trials?', *PI Perspective* (Project Inform San Francisco) 21: 7 (March 1997). Arguing that the trial should never have proceeded in the first place, Project Inform commented: "Some of the brave but unwitting volunteers who participated paid the price with their lives, while others are left with perhaps irreversible immune suppression. In their honour, we must be certain that neither the FDA's traditions nor the doubts of scientists who cannot reason, will ever again be valued over lives of people. The time for studies whose outcome is measured in bodies is over in this epidemic. It has long been over."

Phase I: These trials attempt to translate the data obtained from preclinical and animal studies into the clinical setting. They aim to establish the safe dosage range of a treatment that can be used on a human being. Such trials usually involve a small number of people and if shown to be safe, can proceed to Phase II.

Phase II: These build on the information gained in the earlier studies and evaluate the therapeutic effect of a drug or strategy. In practice, Phase I and II trials are often combined.[8]

Phase III: These are performed when the results of a Phase II trial indicate that a treatment may warrant comparison with the conventional, standard treatment. It is at this stage that randomising and blinding are brought into play to guard against any possible bias in the outcome of the trial. Large numbers of participants are used in this sort of trial.[9]

Phase IV: These trials involve monitoring new therapies in the long term in the general population, where long term or chronic toxicities or effects may be observed. This type of trial is less frequently conducted in Australia.

What are some of the problems with using RCTs to assess HIV/AIDS therapies today?

RCTs have had a troubled history in the HIV/AIDS area. As mentioned earlier, such trials have traditionally been widely regarded as the most reliable source of information on HIV/AIDS therapies. At the same time, their use in HIV/AIDS clinical research has brought to the fore the sorts of concerns that consumers hold about the process. In the recent past, when few antiretroviral treatments were available (and there was very limited access), people with HIV/AIDS and their doctors engaged in activity that effectively (if unintentionally) led to the sabotage of double-blind placebo trails; activity such as unblinding placebos, lying to get on to drug trials, drug sharing and entering multiple trials. Such activity serves to underline the problem of the conflict between the demands of scientific objectivity and the need (and desire) for patients to receive the best possible treatment.

American and European researchers interviewed as part of an AFAO consultancy in 1996 reported that clinical trials designed with a placebo arm would simply lead to problematic results, because participants may have felt compelled to lie about their state of health in order to gain a place in a trial, or they may access to drugs in the underground market if they found they were on an inactive arm.[10]. Restrictions on entry have meant that in previous trials, only those PLWHA with low T cell counts could avail themselves of the drugs being

[8] For example, in early 1994 the National Centre in HIV Epidemiology and Clinical Research started enrolling patients in a very early study (Phase I/II) using a nucleoside analogue manufactured by Wellcome. The study was for 12 weeks and a total of only 40 places were available in selected sites in Australia and Europe. The purpose of the study was to assess whether it was safe to give the new nucleoside analogue (935U83) in combination with the drug ddI. It was also an opportunity to see how participants handled the two drugs together, and to see how the two drugs were absorbed, broken down and removed from the body. (See McKnight Smith, I. (1994), 'New nucleoside in early combination study with ddI', National AIDS Bulletin, 8,3: 42.)

[9] For example, the international Concorde trial was a major Anglo-French trial set up in 1988 to look at whether taking the drug AZT at an earlier stage of HIV gave any benefits to a person with HIV. A total of 1749 people participated in the study. On entry, participants were randomised to a group that started receiving AZT treatment immediately, or to a group that was given a placebo. Here, the placebo was continued until the person started to show symptoms of AIDS or ARC (AIDS-related complex), at which stage AZT was commenced. In 1989, the trial protocol was changed so that anyone on the trial (in either group) who had evidence of an ongoing decline in CD4 cell count below 500 would be allowed to start taking open label AZT, regardless of whether they displayed symptoms of AIDS. (See McKnight-Smith, I. (1994), 'Concorde lands after bumpy ride', National AIDS Bulletin, 8, 4: 40).

[10] Ducket, M. (July 1996), 'Drug Approval, Funding and Clinical Trials: Study Tour'. AFAO: Sydney.

trailed. Access to trials has been severely limited for some groups, particularly women and injecting drug users.

The bottom line for community-based HIV/AIDS organisations is simple: people with HIV/AIDS cannot receive sub-optimal treatment when they participate in clinical trials. However RCTs are not unethical in all circumstances. For example, the AFAO National Treatments Officer, Colin Batrouney, has argued that in some settings, the standard of care arm of a clinical trial could be a good control in, say, trials of new drugs that come on stream.[11] That said, it is important to turn to the unanswered questions about combination therapy, and then look at the possible alternative research methods for answering them.

Unanswered questions about combination therapies

Combination therapies are a relatively recent development, and important questions about how they work remain unanswered. The results of an AFAO questionnaire on research priorities (to which 169 people responded) showed that there was greatest interest in the following research topics:

1. Salvage therapy and immune restoration: "What treatment can restore a severely damaged immune system?"

2. Maintenance therapy: "What do you do about treatment if highly aggressive antiretroviral therapy has successfully reduced your viral load to undetectable levels? Can you reduce or cease treatment?"

3. Resistance[12] tests and their clinical use: "Can you determine whether particular antiretrovirals will work for you before take them?"

The answers to these and other questions may lie in comparisons of combination treatment regimens that meet the 'gold standard' of being maximally suppressive. Dutch clinician Joep Lange has argued that parameters that might distinguish different treatment regimens (or aspects of individual regimens) include: the durability of the antiretroviral effect; the vulnerability of the antiretroviral effect; the antiretroviral effect in sanctuaries for the virus, such as the central nervous system; the availability of subsequent options should a regimen fail; the short- and long-term toxicity; ease of intake and compliance with treatment regimens; quality-of-life measures; cost efficiency; the level of immune reconstitution; and clinical end points, such as survival.[13]

The use of viral load in clinical trials

Viral load is a relatively new way of gauging the effects of antiretroviral therapy. It is a measure of the amount of viral replication in the blood of a person with HIV and it has been demonstrated to be a better indicator of disease progression than the traditional CD4 cell counts. Whereas CD4 cell counts indicate the extent of damage that an immune system has already sustained, viral load indicates the likelihood of that damage occurring. It is therefore an important tool in assessing the effectiveness of antiviral treatments. Two types of test to

[11] Personal communication.
[12] HIV adapts quickly to changing conditions and the development of resistant strains of the virus is a problem. A further complication with combination therapies is the development of cross-resistance, where treatment with one drug creates strains which are resistant to other drugs. This is an important consideration when looking at the options for combination therapy.
[13] Lange, J. M. A. (1997), 'Current problems and the future of antiretroviral drug trials', *Science*, 548-50.

measure viral load are available: the viral culture test and the polymerase chain reaction (PCR) test.

A viral load test result is described in terms of the number of HIV RNA copies per millilitre of blood (copies/ml). In HIV positive people who have not developed symptoms, a viral load greater than 100,000 is considered to be high, and a viral load below 10,000 is considered to be low.[14] Undetectable viral load, increasingly regarded as the gold standard of HIV treatment, refers to measurements that are below the lower limit of a viral load test. People who have very low levels of viral load will be described as having levels that are 'undetectable'. However, this does not mean that HIV is not present; rather, it means that there is a very low level of viral replication. The most accurate viral load test currently available can measure as low as 20 copies per millilitre of blood. As discussed above, viral load levels are considered a good predictor of disease progression, and they are also used as a marker for monitoring the effects of HIV antiretroviral therapy.

Using viral load in trials

Viral load is used as a monitoring tool in different ways in different clinical trials. Previously, trials used clinical endpoints such as death or the development of an AIDS-defining illness as the measurement of the effectiveness of treatment. These "clinical endpoint trials" are designed so that a new drug must prove that it is at least as good as the standard treatment in reducing death or major disease progression in a group of patients.

The ability to measure viral load means that it is possible to judge whether treatment is failing or working much earlier than the point at which a trial participant becomes ill or dies. This has implications for how a trial is designed. Many people in affected communities, and researchers, argue for the greater use of viral load as a "surrogate marker" (in the place of outcomes such as death and disease progression) to let trial participants know how they are responding to treatments. It also means that maintaining an undetectable or other clinically acceptable viral load can be used as the primary way to judge the effectiveness of an antiretroviral drug regimen in a trial. Researchers have also argued that there are potential advantages in using 'time to virologic failure' (as measured by viral load) as a primary endpoint in phase III clinical trials.[15] 'Virologic failure' is defined as an unacceptable level of, or an unacceptable increase in the level of, viral load. The precise definition may vary depending on the context. For example, a compassionate access scheme currently in place for a new HIV drug defines 'virologic failure' as two consecutive viral load test results of greater than 100,000 copies measured more than seven days apart.

In the United States, viral load has been used under "accelerated approval" regulations, which allow drugs to be approved for marketing based on evidence of their ability to reduce viral load and on other surrogate markers. Drugs approved in this way are supposed to be the subject of large, long-term clinical trials to confirm their safety and efficacy.[16] [17] However,

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[14] *National AIDS Manual: HIV and AIDS Treatments Manual*, (September 1997), London: NAM Publications.

[15] A two-day meeting of the Antiviral Drugs Advisory Committee, Center for Drug Evaluation and Research, US Food and Drug Administration, was held in Maryland, July 14-15 1997, and was attended by a representative of Australian Federal administration. A report to committee members attending the conference notes the advantages: "First, this endpoint characterises durability of virologic response. Second, this endpoint permits those participants who have shown loss of virologic response to switch to alternate therapies without jeopardising the study analysis. Finally, studies which allow plasma HIV-RNA monitoring and treatment switches based on lack or loss of virologic response may be appealing to study participants. This could result in more rapid enrolment, increased treatment compliance and increased subject retention."

[16] *AIDS Treatment News,* 270: 3 (1 May 1997).

there is some evidence to suggest that these confirmatory trials are not being conducted. Using viral load instead of clinical endpoints, such as death and the development of AIDS, in confirmatory studies is a debate that also ties in with the funding and approval processes for drugs (and for the tests themselves) in Australia.[18]

An alternative to RCTs

It is important to stress here that randomised control trials will inevitably still have a place in the testing of HIV/AIDS treatments. The challenge is for such trials to take on board the ethical questions raised earlier and also take account of the complex nature of the current treatment regimens. One activist, for example, highlights the need for randomisation to take account of the need for compliance with complex regimens of drugs which require a person with HIV to make major adjustments to his or her lifestyle. In some regimens, for example, PLWHA are required to wake in the middle of the night to take their drugs, as well as fasting for some drugs while taking others with light meals. Thus, a person whose work and other commitments rule out the possibility of adherence to such complex regimens might either be filtered out of the study or alternatively be enrolled in a study arm which brought with it far less complexity.[19]

Lange, in an opinion piece on the future of clinical trials, sets out a number of desirable characteristics for future designs:

- a long follow up period
- flexibility with regard to drug regimens
- comprehensive sampling (that is, sampling not only from blood but also from other tissues, such as lymphatic tissues or tissue sanctuaries such as the central nervous system and genital secretions)
- a strong pharmacology component
- a strong scientific component (he argues that without a good scientific base, it is often better not to do the trial at all)

He argues: "Future trials will thus require the involvement of a rather large multidisciplinary team. These trials will not be large and simple but long, complex and expensive. A cohort study-like approach will allow for maximum utilisation of resources."[20]

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[17]In an interview with AIDS Treatment News (No 273, 20 June 1997), the director of the Division of Antiviral Drug Products of the US Food and Drug Administration, David Feigal, noted: "We have become quite convinced that viral load measures are sensitive enough to detect when a drug regimen is effective, and they are also sensitive enough to detect when a regimen has lost its effectiveness, which can happen from a variety of reasons." Commenting on the potential for new trial designs that use viral load: "The new approach would say that once someone starts on a drug regimen, the first thing we will do is test whether or not that person got an adequate [viral load] response. If not, that is a failure already, and there is no reason for that person to continue to take that particular regimen. And for the participants who get a good response, then of course we want to see how long that response will last."

[18]The Pharmaceutical Benefits Advisory Committee (PBAC) announced in September 1997 that antiretroviral drugs should be made available to PLWHA with a viral load of more than 10,000 copies. Until then, the drugs could only be legally prescribed for PLWHA with less than 500 CD4 cells. In submissions to PBAC, community organisations argued that viral load results were a better indicator of the likelihood of progression to illness. The PBAC recommendation is expected to come into effect from early 1998.

[19]Bill Whittaker, NAPWA National Treatments Spokesperson. Personal communication 13 October 1997.

[20] Lange, J. M. A. (1997), 'Current problems and the future of antiretroviral drug trials', *Science*, 548-50.

Observational databases

In the case of HIV/AIDS treatments, observational databases allow information to be recorded in a way that can measure the effects and outcomes of those treatments. Information is not generated by randomly assigning trial participants to two different groups; rather, the database offers an opportunity to observe the effects of interventions by working from existing medical records or by directly observing people.

Observational studies can be divided into two groups: exploratory and explanatory. Exploratory designs have been described as a sort of 'fishing expedition' to generate hypotheses for further investigation of a more focused kind.[21] Explanatory designs seek to explain the relationship between morbidity or mortality and exposure. These types include: cross-sectional studies (which aim to measure the prevalence of both disease and risk factors simultaneously, in a once-only physical examination or social encounter with the research participants); cohort or prospective studies (where the risk factor or exposure is measured and then one or several follow-ups are conducted to see in whom and when disease or other outcome appears); and case-control or retrospective studies (where the disease is measured first and then the study searches for past exposures).

Such approaches are already used in HIV/AIDS research. A study by Mellors et al[22], looking at the relationship between an individual's viral load and his or her risk of developing AIDS or dying in the future, centred on 1600 asymptomatic HIV-positive gay men who enrolled in the US Multicenter AIDS Cohort Study (MACS) in 1984-85. Blood samples were taken when the men joined the trial, and then at six-monthly intervals. Last year, Mellors et al went back to the samples and tested for viral load, comparing an individual's test results with his medical history. The study concluded that viral load levels are a good predictor of the likelihood of developing AIDS into the future.

Observational databases are best seen as an adjunct to RCTs, rather than alternatives.[23] Researchers have concerns about the evidentiary value of data produced by this method, because statistically the RCT is a superior tool to an observational design. However, observational databases can address some concerns.

Observational databases would be useful in looking at post-exposure prophylaxis, where infection with HIV following exposure to the virus may be interrupted by taking high doses of antiretroviral drugs for a short period of time. Little is currently known about PEP outside the setting of occupational exposure (there is current debate about whether PEP should be made available to people who were exposed to the virus through, say, unprotected sex, or other routes).[24]

Conclusion

The changing landscape of HIV antiretroviral treatments present important challenges to the ways in which information about HIV/AIDS drugs and their effectiveness is gathered.

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[21] Holland, W.W., Detels, R., Knox, G. et al (1991), *Oxford Textbook of Public Health,* vol 2, *Methods of Public Health* (second edition). Oxford: Oxford University Press.

[22] Mellors, J.W. et al (1996), 'Prognosis of HIV-1 infection predicted by the quantity of virus in plasma', *Science,* 272: 1167-70.

[23] Goddard, M. (1996), 'A question of survival: the new challenge of HIV therapy. A report on new developments in HIV therapy and the consequent need for further reform of the drug access and funding systems'. Sydney: AFAO (May 1996).

[24] For a discussion of this debate, see the AFAO Advice Sheet for Members, 'The implications of the availability of HIV Exposure Prophylaxis'. Sydney: AFAO (September 1997).

Enhanced community participation in formulating new trials is important in continuing the sorts of partnerships that have characterised Australia's response to the HIV epidemic to date. At the same time, ongoing and informed debate within the community sector itself is required if the interests and concerns of PLWHA are to be adequately addressed. The CTTAC forum offers such an opportunity.

Viral load tests are vital in allowing people participating in trials to know whether particular combinations of treatments are working for them, and to take action where the treatments are not working. This is crucial, particularly given the potential for resistant strains of the virus to develop. In terms of formally measuring the success or failure of antiretroviral drug regimens in a trial, virologic failure is a preferred measurement to traditional clinical endpoints, such as death and disease progression.

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